(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 November 2004 (25.11.2004)

PCT

(10) International Publication Number
WO 2004/101018 A1

(51) International Patent Classification[7]: A61L 31/12, 31/10, 31/16, 27/34, 27/54, 27/40, 27/44, C08L 33/10, 33/08, 71/02

(21) International Application Number: PCT/US2004/009011

(22) International Filing Date: 23 March 2004 (23.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/431,711 8 May 2003 (08.05.2003) US

(71) Applicant *(for all designated States except US)*: ADVANCED CARDIOVASCULAR SYSTEMS, INC. [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: PACETTI, Stephen, D. [US/US]; 4578 Madoc Way, San Jose, CA 95130 (US). TANG, Yiwen [US/US]; 1230 San Tomas Aquino Road, San Jose, CA 95117 (US).

(74) Agent: WININGER, Aaron; Squire, Sanders & Dempsey L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES

(57) Abstract: A coating for implantable medical devices and a method for fabricating thereof are disclosed. The coating includes a mixture of a hydrophobic polymer and a polymeric hydrophilic additive, wherein the hydrophobic polymer and the hydrophilic additive form a physically entangled or interpenetrating system.

WO 2004/101018 A1

STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES

BACKGROUND

1. Field of the Invention

This invention relates to implantable medical devices such as stents. More particularly, the invention relates to materials that can be used to coat stents.

2. Description of Related Art

In the field of medical technology, there is frequently a necessity to administer drugs locally. To provide an efficacious concentration to the treatment site, systemic administration of medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. For the treatment of vascular lesions, stents can be modified with a polymeric coating to provide local drug delivery capabilities.

Examples of polymers that can be used to coat stents or other implantable devices include hydrophobic polymers, for example, poly(meth)acrylates, such as poly(*n*-butyl methacrylate) (PBMA) and copolymers or terpolymers having units derived from *n*-butyl methacrylate (BMA). PBMA and BMA-based coatings can provide effective control of the rate of release of a drug from a stent. In addition, PBMA and BMA-based polymers are biocompatible, have good adhesion to the underlying stent surface, are easily processable, and possess good physical and mechanical properties such as ability to withstand elongation, compression, and shear that the stent undergoes during crimping onto the catheter, delivery to the lesion site, and expansion.

The properties of PBMA and BMA-based stent coatings can be improved, however. For example, permeability of such coatings can be too low, particularly for drugs having higher molecular weights, leading to potentially insufficient supply of the drug to the diseased site. An ability to better regulate the rate of release through the coatings is desired. The present invention provides such coatings.

BRIEF DESCRIPTION OF DRAWINGS

FIGs. 1-3 are optical micrographs of coatings according to various embodiments of the present invention.

FIG. 4 is a graph illustrating kinetics of in vitro release of a drug through one stent coating of the present invention.

SUMMARY

An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one poly(meth)acrylate and at least one polyalkylene glycol, wherein the macromolecular chains of the poly(meth)acrylate and the polyalkylene glycol form a physically entangled or interpenetrating system. Examples of the poly(meth)acrylate include poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof. Examples of the polyalkylene glycol include poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or interpenetrating system. The hydrophobic polymer can include poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone. The polymeric hydrophilic compound can include polyalkylene glycols, hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

A medical article comprising an implantable substrate and a coating is provided, the coating includes a bulk polymer, an additive polymer in less quantity in the coating that the bulk polymer, the additive polymer being entangled or interpenetrated with the bulk polymer, and a drug.

A method for fabricating a coating for an implantable medical device is provided, the method comprises forming a coating on the device, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or intertwined system.

DETAILED DESCRIPTION

A coating for an implantable medical device, such as a stent, can include an optional primer layer, a drug-polymer layer, and an optional topcoat layer. The drug-polymer layer can be applied directly onto at least a part of the stent surface to serve as a reservoir for an active agent or a drug which is incorporated into the drug-polymer layer. An optional primer layer can be applied between the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent. An optional topcoat layer can be applied over at least a part of the drug-polymer layer to reduce the rate of release of the drug from the reservoir.

The topcoat layer, if used, is the outermost layer of the stent coating. If the topcoat layer is not used, the drug-polymer layer is the outermost layer of the stent coating. The drug-polymer and/or topcoat layer of the stent coating can include at least one hydrophobic polymer. To regulate a rate of release of the drug from the drug-polymer layer the hydrophobic polymer(s) can be physically mixed or blended with at least one polymeric hydrophilic additive to form a polymer system where the macromolecular chains of the hydrophobic polymer and the hydrophobic additive are physically entangled, miscible, and/or interpenetrating. This polymer system can be, in one embodiment, the outermost region or layer of the coating.

Hereinafter, the hydrophobic polymer is also referred to as "polymer," and polymeric hydrophilic additive is also referred to as "additive." The term "physically entangled" is defined hereinafter as a polymer/additive composition in which neither the polymer nor the additive forms a separate phase domain having a size larger than about 100 nanometers, such as the size larger than about 200 nanometers, for example, larger than about 300 nanometers. The size of the domain is determined by the largest linear dimension of the domain particle, e.g., by the diameter of a particle in case the domain particles are spheres. The definition of "physically entangled" also includes a condition that once the polymer and the additive have become physically entangled, they do not disentangle but remain physically entangled for the duration of the service of the coating or until the drug has been released from the coating.

The hydrophobic polymer and the hydrophobic additive are defined hereinafter as "miscible" if the thermogram of the polymer/additive mixture shows substantially no thermal

transitions attributable to either the essentially pure polymer or the essentially pure additive. The thermogram can be obtained by a standard method of thermal analysis known to those having ordinary skill in the art, for example, by the method of differential scanning calorimetry.

The term "interpenetrating" is defined as the polymer/additive system where the polymer and the additive form an interpenetrating polymer network (IPN). The definition of the IPN used by the International Union of Pure and Applied Chemistry (IUPAC) is adopted herein. The IUPAC describes the IPN as a polymer comprising two or more networks which are at least partially interlaced on a molecular scale, to form both chemical and physical bonds between the networks. The networks of an IPN cannot be separated unless chemical bonds are broken. In other words, an IPN structure represents two or more polymer networks that are partially chemically cross-linked and partially physically entangled.

To define the terms "hydrophobic" and "hydrophilic" for the purposes of the present invention, one of the two criteria can be used. According to one criterion, a component in the polymer/additive system (i.e., the polymer or the additive) can be classified by the value of the component's equilibrium water adsorption. Whichever component in the polymer/additive system has the greater value of the equilibrium water adsorption at room temperature is considered hydrophilic and the other component is considered hydrophobic. If more than two components are used in the polymer/additive system, then each can be ranked in order of its equilibrium water adsorption value. In one embodiment, the polymer is considered hydrophobic if it has an equilibrium water adsorption less than 10 mass % at room temperature, and the additive is considered hydrophilic if it has an equilibrium water adsorption at room temperature of 10 mass % or greater.

According to another criterion, a component in the polymer/additive system can be classified by the value of the component's Hildebrand solubility parameter δ. The term "Hildebrand solubility parameter" refers to a parameter measuring the cohesion of a substance and is determined as follows:

$$\delta = (\Delta E/V)^{1/2}$$

where δ is the solubility parameter, $(cal/cm^3)^{1/2}$;

ΔE is the energy of vaporization, cal/mole; and

V is the molar volume, cm^3/mole.

Whichever component in the polymer/additive system has lower δ value compared to the δ value of the other component in the blend is designated as a hydrophobic component, and the other component with higher δ value is designated as hydrophilic. If more than two components are used in the blend, then each can be ranked in order of its δ value. In one exemplary

embodiment, the δ value defining the boundary between the hydrophobic and hydrophilic components of the polymer/additive system can be about 10.7 $(cal/cm^3)^{1/2}$.

Hydrophobic substances typically have a low δ value. In one embodiment, a component in the polymer/additive system that is "hydrophobic" can have a Hildebrand solubility parameter lower than about 10.7 $(cal/cm^3)^{1/2}$. A component in the polymer/additive system that is "hydrophilic" can have a solubility parameter greater than about 10.7 $(cal/cm^3)^{1/2}$.

To make the polymer/additive mixture, the polymer can be blended with the additive and the blend can be dissolved in a solvent or in a system comprising a mixture of solvents. The term "dissolved" means that the polymer/additive blend, when combined with a suitable solvent or a mixture of solvents, is capable of forming a system which can be applied on a stent by a common technique, such as spraying or dipping. The solvent or a mixture of solvents can be selected by those having ordinary skill in the art depending, among other factors, on the nature of the polymer and the additive.

The polymer/additive solution can be then applied on the stent by a commonly known technique known to those having ordinary skill in the art, for example, by spraying or dipping, followed by drying, for example, by baking. The polymer/additive solution can be used to form the topcoat layer and/or the drug-polymer layer of the stent coating.

The combined mass concentration of the polymer and the additive in the polymer/additive solution can be between about 1% and about 10%, for example, about 2%. A ratio between the hydrophobic polymer and the polymeric hydrophilic additive in the polymer/additive solution can be between about 99:1 and about 9:1, such as between about 74:1 and about 14:1, more narrowly between about 49:1 and about 19:1. For example, for a polymer/additive solution containing about 2 mass % of the hydrophobic polymer, the concentration of the polymeric hydrophilic additive can be between about 0.04 and about 0.1 mass % of the total mass of the solution.

The polymer/additive solution can be prepared by various alternative methods. For example, the hydrophobic polymer and the polymeric hydrophilic additive can be dissolved separately to obtain a hydrophobic polymer solution and a polymeric hydrophilic additive solution, followed by combining the two solutions to form the polymer/additive solution. Alternatively, the hydrophobic polymer can be dissolved first to form the hydrophobic polymer solution, followed by adding the polymeric hydrophilic additive to the hydrophobic polymer solution to form the polymer/additive solution. As another alternative, the additive can be dissolved first to form the additive solution followed by adding the polymer to form the polymer/additive solution.

Examples of hydrophobic polymers include poly(meth)acrylates. The term "poly(meth)acrylates" refers to both polymethacrylates and polyacrylates. Examples of poly(meth)acrylates that can be used include homo-and copolymers of butyl methacrylate, for example PBMA, poly(vinylidene fluoride-co butyl methacrylate), or poly(methyl methacrylate-co-butyl methacrylate). Representative examples of other hydrophobic polymers that can be used in practice of the present invention include the following polymers and mixtures thereof:

(a) poly(meth)acrylates other than PBMA or BMA-based polymethacrylates, such as poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), and poly(*iso*-butyl acrylate);

(b) vinyl polymers such as poly(ethylene-co-vinyl alcohol), for example, poly(ethylene-co-vinyl alcohol) having a molar content of ethylene-derived units of at least 44 %, poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-co-styrene) terpolymers;

(c) polyolefins, for example, atactic polypropylene;

(d) halogenanated (e.g., fluorinated or chlorinated) polymers such as poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), various grades of amorphous TEFLON (including polytetrafluoroethylene) available from E.I. Du Pont de Nemours & Co., poly(vinyl chloride), and poly(vinylidene chloride);

(e) polymers having urethane groups, such as polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, and silicone urethanes; and

(f) polybutyrals, nylon, silicones, polycarbonate, and polysulfone.

Representative examples of polymeric hydrophilic additives that can be used in practice of the present invention include hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, poly(ethylene glycol)(PEG), poly(ethylene oxide), poly(propylene glycol), PLURONIC, TETRONIC, poly(trimethylene glycol), poly(tetramethylene glycol), polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers such as poly(vinylmethyl ether) or poly(vinylethyl ether);

gelatin, collagen, albumin, chitin, heparin, elastin, fibrin and mixtures thereof. PLURONIC is a trade name of a poly(ethylene oxide-co-propylene oxide). TETRONIC is a trade name of a family of non-ionic tetrafunctional block-copolymer surfactants. PLURONIC and TETRONIC are available from BASF Corp. of Parsippany, New Jersey.

To achieve the physical entanglement of the hydrophobic polymer and polymeric hydrophilic additive, at least one polymer and at least one additive can be blended together in a common solvent system that includes at least one very volatile solvent, followed by applying the solution onto a stent, for example, by spraying. As used herein, "very volatile solvent" means a solvent that has a vapor pressure greater than 30 Torr at ambient temperature. Examples of very volatile solvent include acetone and methyl ethyl ketone. Alternatively, to physically entangle the hydrophobic polymer and polymeric hydrophilic additive, the polymer and the additive can be blended in the melt, and then applied to the stent from the melt, for example by curtain coating.

One way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive is by blending the polymer and the additive in a solvent, or solvent blend, in which both components are soluble. The solution can be applied onto a stent, for example, by spraying, followed by the removal of the solvent by drying. For the polymer and the additive which are capable of forming an interpenetrating system, the polymers and the additive are expected to interpenetrate while still in solution, and to remain interpenetrated upon solvent removal.

Alternatively, to form an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, the polymer and additive, which can be polymerized according to two different mechanisms, can be selected. For example, the hydrophobic component can be a carbonate urethane that is polymerized by condensation reactions between isocyanate and hydroxyl groups, while the hydrophilic additive can be poly(2-hydroxyethyl methacrylate) that polymerizes by a free radical mechanism. The monomers may be dissolved in a common solvent system, applied to the stent, and then polymerized directly on the stent.

As another alternative way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, a high molecular weight polymer and additive can be selected, each component having reactive or associative groups that can interact with the reactive or associative groups of the other component. For example, such hydrophilic additive as hydroxy terminated PEG can be blended with a high molecular weight, hydrophobic polyurethane with active isocyanate groups along the backbone. The additive and the polymer can be blended in solution, sprayed onto a stent, followed by curing. Although sometimes the

two components may be not miscible, the covalent bonds between them can still prevent phase separation.

To facilitate the formation of an entangled and/or interpenetrating hydrophobic polymer-polymeric hydrophilic additive system, the polymer and the additive can be selected in such a way that the chain lengths of the polymer and the additive, as determined by degree of polymerization, are such as to promote the entanglement and/or interpenetration of the macromolecules of the polymer and the additive. The term "degree of polymerization" refers to a number of repeating monomeric units in a single macromolecule. The chain lengths that promote the formation of an entangled and/or interpenetrating network can be such that the contour length of the hydrophilic additive lies in the range of between about 10% and about 100% of the contour length of the hydrophobic polymer, for example, between 50% and 100%, such as 80%. The term "contour length" refers to the combined length of all bonds along the main chain (the backbone) of a macromolecule. The contour length can be approximated as the degree of polymerization multiplied by the number of bonds in the repeat unit. An average bond length of about 1.4 Å can be used for the computation. The following example can be used to illustrate how the molecular weights of the polymer and the additive can be chosen to achieve a proper ratio between the contour lengths of the polymer and the additive.

PBMA with a number-averaged molecular weight (M_n) of about 200,000, has a degree of polymerization of 1,408 and has 2 bonds in the polymer backbone per repeat unit. Thus, a contour length of a PBMA macromolecule is about 3,940 Å. Suitable hydrophilic additive to achieve entanglement can be PEG having contour lengths between about 394 Å and about 3,940 Å. PEG has 3 bonds per repeat unit, so for PEG having contour lengths between about 394 Å and about 3,940 Å, corresponding degree of polymerization is approximately between 131 and 1,313, and the corresponding M_n is between about 5,780 and about 57,800.

Generally, M_n of the hydrophobic polymer can be between about 50,000 and 1000,000 Daltons, for example, about 100,000 Daltons. The molecular weight of the hydrophilic additive can be between about 5,000 and about 100,000 Daltons, for example, about 40,000 Daltons. If PBMA is used as the hydrophobic polymer, the molecular weight of PBMA can be between about 100,000 and about 300,000 Daltons, for example, about 200,000 Daltons. If PEG is used as the hydrophilic additive being mixed with PBMA, the molecular weight of PEG can be between about 10,000 and about 60,000 Daltons, for example, about 20,000 Daltons.

The embodiments of the present invention are described in connection with a stent, e.g., balloon expandable or self-expandable stents; however, other implantable medical devices can also be coated. Examples of such implantable devices include stent-grafts, grafts (e.g., aortic

grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corp. of Santa Clara, California). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. The device itself can be made in whole or in part from the disclosed polymeric blends.

For the drug-polymer layer, the coating can include an active agent or a drug. The drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The drug could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of drugs include antiproliferative substances such as actinomycin D, or derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wisconsin, or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I_1, actinomycin X_1, and actinomycin C_1. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL® by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere®, from Aventis S.A., Frankfurt, Germany), methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin® from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin® from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and

thrombin inhibitors such as Angiomax ™ (Biogen, Inc., Cambridge, Mass.). Examples of such cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and donors of nitric oxide. An example of an antiallergic agent is permirolast potassium. Other therapeutic substances or agents which may be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus, dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as 40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, and 40-O-tetrazole-rapamycin.

The molecular weight of the drug can influence the choice of the molecular weights of the polymer and the additive, as well as the ratios between the polymer and the additive, since the release rate of the drugs having higher molecular weights is expected to be slower compared with the release rate of the drugs with lower molecular weights. To illustrate, when the PBMA/PEG topcoat system is used in conjunction with EVEROLIMUS (having molecular weight 958 Daltons), M_n of PBMA can be between about 90,000 Daltons and about 300,000 Daltons, for example, about 190,000 Daltons and M_n of PEG can be between about 6,000 Daltons and about 20,000 Daltons, for example, about 18,000 Daltons, and the mass ratio between PBMA and PEG can be between about 49:1 and about 9:1, for example, about 20:1. At the same time, in the case of estradiol (having molecular weight of 272), M_n of PBMA can be between about 150,000 Daltons and about 900,000 Daltons, for example, about 300,000 Daltons and M_n of PEG can be between about 10,000 Daltons and about 50,000 Daltons, for example, about 30,000 Daltons, and the mass ratio between PBMA and PEG can be between about 99 :1 and about 25:1, for example about 49:1.

Embodiments of the present invention are further illustrated by the following examples.

Example 1

A first polymer solution was prepared, the solution containing:

(a) about 5 mass % of poly(*n*-butyl methacrylate) (PBMA) having M_n of about 154,000; and

(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

A second polymer solution was prepared, the solution containing:

(a) about 5 mass % of poly(ethylene glycol) (PEG) having M_n of about 18,000; and

(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

The first polymer solution was combined with the second polymer solution to prepare a PBMA/PEG solution. The amount of the first and second polymer solutions were selected to obtain the PBMA/PEG solution having a mass ratio between PBMA and PEG of about 49:1.

The PBMA/PEG solution was cast on a glass slide, and the solvent was removed by drying at room temperature followed by baking at about 80°C for about 1 hour. As a result, an adhered polymer film was formed on the glass slide. An optical micrograph of the dry PBMA/PEG film was taken in transmitted polarized light, as shown by FIG. 1. Under such light, amorphous polymers appear dark and crystalline polymers appear bright. As seen from FIG. 1, the PBMA/PEG system appears uniformly dark showing good miscibility of PBMA and PEG. FIG. 1 does not show that PEG forms a separate phase.

Example 2

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio between PBMA and PEG in the PBMA/PEG solution was about 19:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. 2. As seen from FIG. 2, the PBMA/PEG system appears mostly uniform, with some amount of the crystalline phase formed by PEG represented by bright spots on the micrograph.

Example 3

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio between PBMA and PEG in the PBMA/PEG solution was about 10:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. 3. As seen from FIG. 3, the PBMA/PEG system includes visible crystalline areas. Compared with the film described in Example 2, the film shown by FIG. 3 included more substantial amount of the crystalline phase formed by PEG.

Example 4

A first composition was prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % of poly(ethylene-co-vinyl alcohol) (EVAL); and

(b) the balance, DMAC solvent.

The first composition was applied onto the surface of a bare 18 mm VISION stent (available from Guidant Corp.) by spraying and dried to form a primer layer. A spray coater was used, having a 0.014 fan nozzle maintained at about 60°C with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). About 70 μg of the wet coating was applied. The wet coating was baked at about 140°C for about 2 hours, yielding a dry primer layer.

A second composition was prepared by mixing the following components:

(a) about 2.0 mass % of EVAL;

(b) about 1.6 mass % of EVEROLIMUS; and

(c) the balance, DMAC solvent.

The second composition was applied onto the dried primer layer to form a drug-polymer layer, using the same spraying technique and equipment used for applying the primer layer. About 300 μg of the wet coating was applied, followed by drying, e.g., by baking as described above. The dry drug-polymer layer contained about 130 μg of EVEROLIMUS.

A third composition was prepared by mixing the following components:

(a) about 2 mass % of PBMA having M_n of about 154,000; and

(b) about 0.1 mass % of PEG having M_n of about 18,000; and

(c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

The third composition was applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating was applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat was about 50 μg.

The kinetics of release of EVEROLIMUS *in vitro* was studied chromatographically (HPLC). To study the kinetics, three stents were coated as described above in this Example. The results of this study are illustrated by the chart shown by FIG. 4. The amount of EVEROLIMUS released from a stent coating having the PBMA-PEG topcoat was measured (curve 1). The average of the data obtained from the three stents was used to plot curve 1. As a control, two identical control stents were used, except the topcoat included only pure PBMA instead of PBMA-PEG. The control curve 2 was plotted using the average of the data obtained

from the two control stents. As seen from FIG. 4, the rate of release of EVEROLIMUS through the PBMA-PEG topcoat is about twice the rate of release through the PBMA topcoat.

Example 5

A primer and drug-polymer layers can be formed on a stent as described in Example 4, but instead of EVEROLIMUS, rapamycin can be used. A topcoat composition can then be prepared by mixing the following components:

(a) about 2 mass % of PBMA having M_n of about 154,000; and

(b) about 0.05 mass % of PEG having M_n of about 18,000;

(c) about 0.05 mass % of poly(propylene glycol) (PPG) having M_n of about 40,000; and

(c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

If desired, poly(tetramethylene glycol) (PTMG) can be used in the topcoat composition instead of PPG. The M_n of PTMG can also be about 40,000. A PPG/PTMG blend having any ratio between PPG and PTMG can also be optionally used instead of PPG. In this example, in the topcoat composition the mass ratio between PEG and PPG is 1:1. If desired, the amount of PPG or PTMG, or a mixture thereof can be up to about twice amount of PEG. Optionally, all of the PEG in the topcoat composition can be replaced with PPG or PTMG, or with a mixture thereof.

The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg.

Example 6

A primer and drug-polymer layers can be formed on a stent as described in Example 4. A topcoat composition can then be prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 1.9 mass % of poly(hexafluoropropene-co-vinylidene fluoride) (PHFP-VDF) having M_n about 125,000.

(b) between about 0.04 mass % and about 0.8 mass %, for example, about 0.1 mass % of F127 PLURONIC copolymer; and

(c) the balance, a mixture of solvents, the solvent mixture including acetone and cyclohexanone in a mass ratio of about 1:1.

F127 PLURONIC is a difunctional poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer terminating in primary hydroxyl groups. F127 PLURONIC has M_n of about 12,600.

The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg.

While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

WHAT IS CLAIMED IS:

1. An implantable medical device comprising a coating, the coating including a mixture of at least one poly(meth)acrylate and at least one polyalkylene glycol, wherein the macromolecular chains of the poly(meth)acrylate and the polyalkylene glycol form a physically entangled or interpenetrating system.

2. The device of Claim 1, wherein the device is a stent.

3. The device of Claim 1, wherein a ratio between the poly(meth)acrylate and the polyalkylene glycol is between about 99:1 and about 9:1.

4. The device of Claim 1, wherein the poly(meth)acrylate is selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

5. The device of Claim 1, wherein the polyalkylene glycol is selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

6. The device of Claim 1, wherein the coating additionally comprises a drug.

7. The device of Claim 6, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

8. An implantable medical device comprising a coating, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or interpenetrating system.

9. The device of Claim 8, wherein the device is a stent.

10. The device of Claim 8, wherein the hydrophobic polymer has a Hildebrand solubility parameter lower than about 10.7 $(cal/cm^3)^{1/2}$.

11. The device of Claim 8, wherein the hydrophobic polymer has an equilibrium water adsorption less than about 10 mass % at room temperature.

12. The device of Claim 8, wherein the hydrophobic polymer comprises poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

13. The device of Claim 12, wherein the poly(meth)acrylates are selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

14. The device of Claim 12, wherein the vinyl polymers are selected from a group consisting of poly(ethylene-co-vinyl alcohol), poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-co-styrene) terpolymers, and mixtures thereof.

15. The device of Claim 12, wherein the polyolefin is atactic polypropylene.

16. The device of Claim 12, wherein the halogenanated polymers are selected from a group consisting of poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), polytetrafluoroethylene, poly(vinyl chloride), poly(vinylidene chloride), and mixtures thereof.

17. The device of Claim 12, wherein the polymers having urethane groups are selected from a group consisting of polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, silicone urethanes, and mixtures thereof.

18. The coating of Claim 8, wherein the polymeric hydrophilic compound is selected from a group consisting of polyalkylene glycols, hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

19. The device of Claim 18, wherein the polyalkylene glycols are selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol),

poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

20. The device of Claim 8, wherein the ratio between the hydrophobic polymer and the polymeric hydrophilic additive is between about 99:1 and about 9:1.

21. The device of Claim 8, wherein the coating additionally comprises a drug.

22. The device of Claim 21, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

23. A medical article comprising an implantable substrate and a coating, the coating including:

(a) a bulk polymer;

(b) an additive polymer in less quantity in the coating that the bulk polymer, the additive polymer being entangled or interpenetrated with the bulk polymer; and

(c) a drug,

wherein the additive polymer changes the rate of release of the drug from the coating.

24. The medical article of Claim 23, wherein by increasing the ratio of the additive polymer to the bulk polymer, the rate of release of the drug is increased.

25. The medical article of Claim 23, wherein the bulk polymer is more hydrophobic that the additive polymer.

26. The medical article of Claim 23, wherein the bulk polymer includes a poly(meth)acrylate.

27. The medical article of Claim 23, wherein the poly(meth)acrylate is selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

28. The medical article of Claim 23, wherein the additive polymer includes a polyalkylene glycol.

29. The medical article of Claim 28, wherein the polyalkylene glycol is selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

30. The medical article of Claim 23, wherein the contour length of the additive polymer is between about 10% and about 100% of the contour length of the bulk polymer.

31. A method of fabricating a coating for an implantable medical device, comprising forming a coating on the device, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or intertwined system.

32. The method of Claim 31, wherein the device is a stent.

33. The method of Claim 31, wherein the hydrophobic polymer has a Hildebrand solubility parameter lower than about 10.7 $(cal/cm^3)^{1/2}$.

34. The method of Claim 31, wherein the hydrophobic polymer has an equilibrium water adsorption less than about 10 mass % at room temperature.

35. The method of Claim 31, wherein the hydrophobic polymer comprises poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

36. The method of Claim 35, wherein the poly(meth)acrylates are selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

37. The method of Claim 35, wherein the vinyl polymers are selected from a group consisting of poly(ethylene-co-vinyl alcohol), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, poly(styrene-co-butadiene-co-styrene) terpolymers, and mixtures thereof.

38. The method of Claim 35, wherein the polyolefin is atactic polypropylene.

39. The method of Claim 35, wherein the halogenanated polymers are selected from a group consisting of poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), polytetrafluoroethylene, poly(vinyl chloride), poly(vinylidene chloride), and mixtures thereof.

40. The method of Claim 35, wherein the polymers having urethane groups are selected from a group consisting of polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, silicone urethanes, and mixtures thereof.

41. The method of Claim 31, wherein the polymeric hydrophilic compound is selected from a group consisting of polyalkylene glycols, hyaluronic acid, chondroitan sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

42. The method of Claim 41, wherein the polyalkylene glycols are selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

43. The method of Claim 31, wherein a ratio between the hydrophobic polymer and the polymeric hydrophilic additive is between about 99:1 and about 9:1.

44. The method of Claim 31, wherein the coating additionally comprises a drug.

45. The device of Claim 44, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

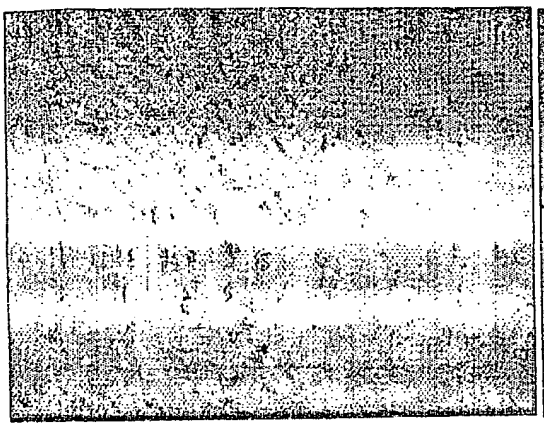

FIG. 1

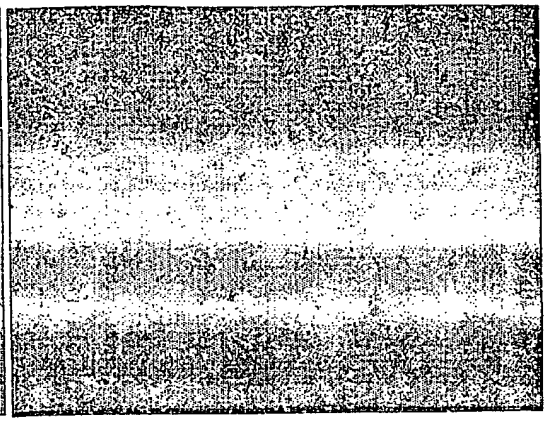

FIG.2

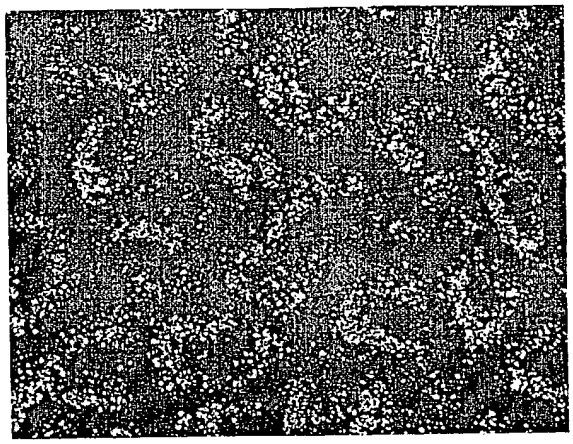

FIG. 3

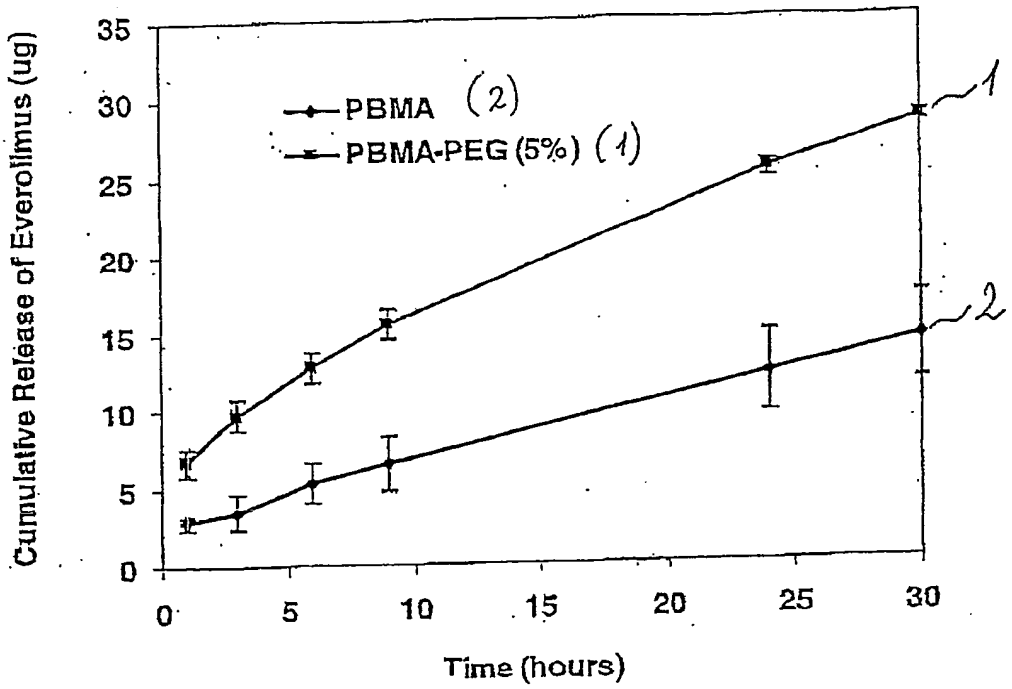
Cumulative Release of Everolimus (ug)
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time (hours)
PBMA (2)
PBMA-PEG (5%) (1)
1
2

FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/12 A61L31/10 A61L31/16 A61L27/34 A61L27/54
A61L27/40 A61L27/44 C08L33/10 C08L33/08 C08L71/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 120 904 A (DING NI ET AL) 19 September 2000 (2000-09-19) column 16, line 43 - line 65 column 17, line 17 - line 47 column 32, line 28 - line 36	8-12, 17-19, 31-35, 40-42
X	US 2002/133183 A1 (LENTZ DAVID CHRISTIAN ET AL) 19 September 2002 (2002-09-19) page 6, paragraph 69 page 7, paragraph 71 page 9, paragraph 87 page 18, paragraph 165	8-12,16, 18-27, 31-35, 39,41-45

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2004	05/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Staber, B

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 110 483 A (ZHANG XIANPING ET AL) 29 August 2000 (2000-08-29) column 2, line 13 - line 25 column 3, line 37 - line 42 column 3, line 45 - line 56	8-14, 18-21, 23-29, 31-37, 41-44
P,X	WO 2004/010975 A (SCIMED LIFE SYSTEMS INC) 5 February 2004 (2004-02-05) page 6, paragraph 29 page 9, paragraph 38 page 10, paragraph 44 claims 2-5,7	8-12,14, 18,19, 21,23, 31-35, 37,41, 42,44
X	US 590 263 A (BOSTON SCIENT LTD (BB)) 11 May 1999 (1999-05-11) column 4, line 47 - line 54 example 3	1,2,5,6, 8,31
A	US 2002/065551 A1 (BINDERMAN ITZHAK ET AL) 30 May 2002 (2002-05-30) page 3, paragraph 34 page 3, paragraph 37	1-45
P,A	WO 2004/009145 A (ADVANCED CARDIOVASCULAR SYSTEM) 29 January 2004 (2004-01-29) abstract	1-45

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6120904 A	19-09-2000	US 5919570 A	06-07-1999
		CA 2211643 A1	08-08-1996
		DE 69613104 D1	05-07-2001
		DE 69613104 T2	07-03-2002
		EP 0808223 A1	26-11-1997
		WO 9623601 A1	08-08-1996
		JP 3357064 B2	16-12-2002
		JP 10502855 T	17-03-1998
US 2002133183 A1	19-09-2002	US 2002165608 A1	07-11-2002
		US 2001029351 A1	11-10-2001
		AU 9486901 A	08-04-2002
		CA 2424029 A1	04-04-2002
		EP 1322235 A1	02-07-2003
		JP 2004521668 T	22-07-2004
		WO 0226139 A1	04-04-2002
		US 2003065377 A1	03-04-2003
		US 2003065345 A1	03-04-2003
		US 2003065346 A1	03-04-2003
		AU 1129902 A	08-04-2002
		AU 1132102 A	08-04-2002
		CA 2424038 A1	04-04-2002
		CA 2424049 A1	04-04-2002
		CA 2450962 A1	03-01-2003
		EP 1322351 A1	02-07-2003
		EP 1322342 A1	02-07-2003
		EP 1406682 A1	14-04-2004
		JP 2004518458 T	24-06-2004
		WO 0226281 A1	04-04-2002
		WO 0226271 A1	04-04-2002
		WO 03000308 A1	03-01-2003
		US 2004102758 A1	27-05-2004
		US 2002111590 A1	15-08-2002
		US 2002051730 A1	02-05-2002
		AU 7730201 A	11-04-2002
		AU 9316101 A	08-04-2002
		CA 2357881 A1	29-03-2002
		CA 2425753 A1	04-04-2002
		CN 1477980 T	25-02-2004
		EP 1192957 A2	03-04-2002
		EP 1335761 A1	20-08-2003
		JP 2002238994 A	27-08-2002
		WO 0226280 A1	04-04-2002
		US 2002094440 A1	18-07-2002
		CA 2408754 A1	22-11-2001
		JP 2004504078 T	12-02-2004
		WO 0187375 A1	22-11-2001
US 6110483 A	29-08-2000	AU 8159898 A	04-01-1999
		CA 2293370 A1	30-12-1998
		CN 1261288 T	26-07-2000
		EP 1003571 A2	31-05-2000
		JP 2002506369 T	26-02-2002
		WO 9858690 A2	30-12-1998
WO 2004010975 A	05-02-2004	US 2004022824 A1	05-02-2004
		WO 2004011055 A2	05-02-2004
		WO 2004010975 A2	05-02-2004

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004010975 A		US 2003224033 A1	04-12-2003
US 590263 A		NONE	
US 2002065551 A1	30-05-2002	AU 2095002 A WO 0224249 A2	02-04-2002 28-03-2002
WO 2004009145 A	29-01-2004	WO 2004009145 A1	29-01-2004